

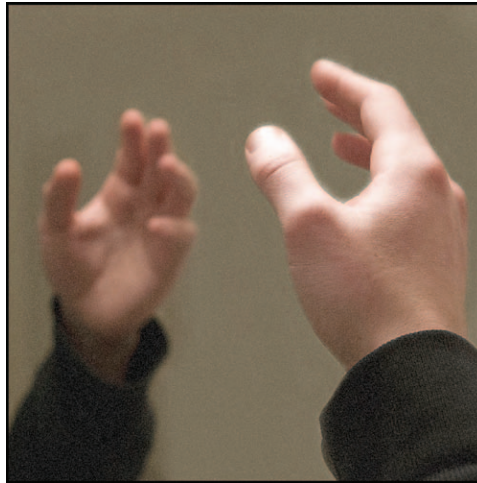
# Complex Generalized Instead of Complex Regional?

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FOR more than 100 yr, the pain community has puzzled over what we now call complex regional pain syndrome (CRPS), and this contemplation seems to have been scientifically productive, given that a PubMed search using the CRPS keywords returns 4,862 results (as of January 21, 2014) with a steadily increasing number of publications over the last 20 yr. One result of this research is a lively scientific discussion whether the main pathophysiology of CRPS has to be looked for in the peripheral or the central nervous system.

In this issue of *ANESTHESIOLOGY*, Terkelsen *et al.*<sup>1</sup> have added another chapter to this story: Generalized central sensitization as indicated by bilateral hyperalgesia to various painful stimuli in patients with CRPS. To investigate the function of the peripheral nervous system, the authors tested thermal sensation, sympathetic reflexes, and capsaicin-evoked flare responses and did not observe any differences between patients and controls. On the basis of their results, the authors concluded that CRPS is not regional, rather it is a generalized central pain syndrome, and peripheral changes might be of minor importance. However, in the first months after onset clinical observation of patients with CRPS very often reveals all signs of inflammation as defined by early Galen: reddening (rubor), pain/hyperalgesia (dolor), edema (tumor), temperature increase (calor), and loss of function (functio laesa). In addition, there is localized proliferation of fibroblasts, bone cells, and hairs.

First of all, we would like to commend the authors for their comprehensive study and the clear presentation of their results—from a group of mainly chronic patients with CRPS. However, as indicated above, we doubt that these results are generalizable to all patients with CRPS. This raises two questions: “What is CRPS?” and “What is central sensitization in CRPS?” We believe that one could be as diverse as the other and that many central findings in CRPS follow the peripheral changes.



***“We should leave behind categorizations that lump together too many pathophysiologies and bring too much variation into scientific studies—we must be more specific.”***

We would like to discuss these points:

1. CRPS starts with *peripheral* trauma (see table 1 in the study by Terkelsen *et al.*<sup>1</sup>). Before that, the patients would have been control subjects. There is no indication of a preexisting chronic pain phenotype. The first consequence of this trauma is a visible, regional, and unilateral exaggerated inflammatory response of the affected limb. In acute CRPS, there are no visible contralateral signs or loss of function but also no contralateral quantitative sensory testing findings unequivocally indicating central sensitization, even compared with controls.<sup>2</sup> The situation is different if acute CRPS becomes chronic after a few months. In a patient group with the same demographic characteristics as in the current study, Hugel *et al.*<sup>3</sup> demonstrated hyperalgesia in response to all painful stimuli of the quantitative sensory testing test battery on the contralateral side, which was also interpreted as central sensitization.
2. We have also gathered plenty of objective evidence for the above-mentioned unilateral exaggerated inflammatory response in acute CRPS. There are unilateral increased inflammatory cytokines in suction blisters, there is unilateral increased bone metabolism in scintigraphy, and very recently, we could directly demonstrate an overproduction of cytokines in keratinocytes from the affected limb, a proliferation of these keratinocytes, and an increased number of mast cells in the skin—in acute CRPS of 3 months duration or less. In chronic CRPS (up to 8 yr duration), the findings were just the opposite, for example, reduced epidermal thickness.<sup>4</sup>
3. Any inflammation has a neurogenic component. The inflammatory mediators sensitize the abundant but physiologically insensitive (chemo-) peptidergic nociceptors, which then respond to physiological stimuli (mechanical

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and thermal) by the release of neuropeptides. These neuropeptides augment the visible signs of inflammation in acute CRPS: edema, vasodilation, hair growth, but also sweating.<sup>5</sup> Neuropeptide release after stimulation is unilaterally and indicated by worsening of the inflammatory symptoms on the affected side,<sup>6</sup> but the biological activity of the released neuropeptides may be bilaterally increased because of hampered inactivation, for example, by drugs. The neuropeptides themselves do not seem to be very important for pain or nociceptor sensitization, rather are a surrogate of nociceptor activation and contribute to tissue repair, as intradermal application of neuropeptides does not cause any sensation.<sup>7</sup> In chronic CRPS when inflammatory signs have subsided, epidermal fiber loss has been directly observed<sup>8</sup> indicating ongoing localized peripheral pathology. This fiber loss might contribute to the atrophic changes of the skin as reported above. However, its contribution to the other signs of chronic CRPS is undetermined.

There are a number of ways peripheral changes can develop into something that we call centralized in CRPS, but in fact may not involve changes within the central nervous system as a driving force. Bilateral central nociceptive sensitization (as defined by quantitative sensory testing hyperalgesia) has been described in various pain diseases, for example, in whiplash patients, in radicular and nonradicular lower back pain,<sup>9</sup> and in fibromyalgia. In particular, fibromyalgia is a very good example that these ostensibly central findings are not necessarily specific to central nervous system mechanisms. A significant proportion of these patients had peripheral small-fiber pathology.<sup>10</sup> The inflammatory mediators and neuropeptides in localized CRPS (shown also for migraine) spill over from the local release site into the circulation, which might cause spinal sensitization such as mechanical hyperalgesia.<sup>11</sup> From focal brain damage, we know that the exposure of neuronal tissue to the circulation could lead to autoimmune encephalopathies. In posttraumatic CRPS (local damage to the peripheral nervous system), we found autoantibodies to sympathetic structures in the serum,<sup>12</sup> which may have systemic effects. In all of these cases, it is the periphery that drives the central symptoms.

We have written this controversial comment to encourage all CRPS researchers, ourselves included, to move a step forward. We should leave behind categorizations that lump together too many pathophysiologies and bring too much variation into scientific studies—we must be more specific. Headache researchers and the headache classification (which is to some extent arbitrary but very useful for research) should be paragons. In clinical practice, however, complexity is the rule. Terkelsen *et al.* must be thanked for adding another piece to this complex puzzle—a generalized central piece.

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